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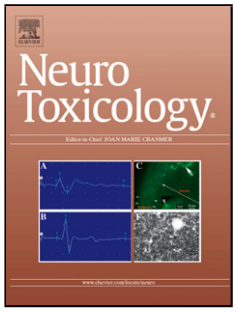

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Aldehyde Dehydrogenase 2 in the spotlight: the link between mitochondria and neurodegeneration

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Highlights

- Neurodegenerative diseases are threatening conditions that affect life-quality and life-span of the affected patients.
- ALDH2 is a critical enzyme involved in neurotoxic mechanisms of PD and AD
- 4-HNE which is considered one of the fundamental signaling molecules in the pathogenesis of AD and its detoxification depend on ALDH2 activity.
- ALDH2 activation is proposed as a therapeutic approach for PD, since the enzyme plays a crucial role in mitochondrial normal function maintenance that protects against neurotoxicity.

Abstract: Growing body of evidence suggests that mitochondrial dysfunctions and resultant oxidative stress are likely responsible for many neurodegenerative diseases, including Alzheimer´s disease (AD) and Parkinson´s disease (PD). Aldehyde dehydrogenase (ALDH) superfamily plays a crucial role in several biological processes including development and detoxification pathways in the organism. In particular, ALDH2 is crucial in the oxidative metabolism of toxic aldehydes in the brain, such as catecholaminergic metabolites (DOPAL and DOPEGAL) and the principal product of lipid peroxidation process 4-HNE. This review aims to deepen the current knowledge regarding to ALDH2 function and its relation with brain-damaging processes that increase the risk to develop neurodegenerative disorders. We focused on relevant literature of what is currently known at molecular and cellular levels in experimental models of these pathologies. The understanding of ALDH2 contributions could be a potential target in new therapeutic approaches for PD and AD due to its crucial role in mitochondrial normal function maintenance that protects against neurotoxicity.

Keywords: Aldehyde dehydrogenase 2; mitochondrial dysfunction; Alzheimer´s Disease; Parkinson´s Disease; oxidative stress

Abbreviations

4-HNE, 4-hydroxy2-nonenal; ACD, acetaldehyde; AD, Alzheimer´sDisease; ALDH, aldehydedehydrogenase; ALDH1A1, aldehyde dehydrogenase1A1; ALDH2, aldehydedehydrogenase 2; APOE ε4, apolypoprotein E ε4; APP, amyloid precursor protein; AR, aldehydereductase; ATP, adenosinetriphosphate; COMT, catechol o-metyltransferase; CSF, cerebrospinal fluid; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; DOPAL, 3,4-dihydroxyphenylacetaldehyde; DOPEGAL, 3,4-dihydroxyphenylglycolaldehyde; EPI, epinephrine; ER, endopolasmicreticulum; GWAS, genome-wideassociationstudies; HVA, homovanilicacid; MAO –B, monoaminoxidasetype; MDA, malondialdehyde; NAD, nicotine; NE, norepinephrine; OB, olfactorybulb; OE, olfactoryepithelium; PD, Parkinson´sDisease; PT, permeabilitytransition; ROS, reactive oxygenspecies; RAS, reactive aldehydespecies; SN, substantianigra; UV, ultraviolet light

Introduction

Ample evidence suggests that mitochondrial dysfunctions are likely responsible for many neurodegenerative diseases, especially Alzheimer´s disease (AD) and Parkinson´s disease (PD). The variety of symptoms expressed in these neuropathologies may obey to the increase in cell death processes as consequence of early several mitochondrial disorders such as a deficient production of adenosine triphosphate (ATP), an increase in the release of proapoptotic factors and reactive oxygen species (ROS) generation, which increase oxidative stress susceptibility (Bhat et al., 2015). One of the consequences of this excessive oxidative stress status is the production of reactive and toxic aldehydes by lipid peroxidation from the membrane-rich mitochondria (Chen et al., 2016). Aldehydes have a reactive and electrophilic nature and commonly form adducts with macromolecules, but is also ubiquitous in the cell microenvironment, acquiring a toxic connotation. These toxic aldehydes are generated by the endogenous metabolism of neurotransmitters, amino acids, and lipids (Marchitti et al., 2007). Among them, lipid peroxidation-derived α, β-unsaturated aldehydes such as 4-hydroxynonenal (4-HNE), malondialdehyde (MDA), acrolein, acetaldehyde, 3,4-dihydroxyphenylacetaldehyde (DOPAL, MAO product of dopamine) and 3,4-dihydroxyphenylglycoaldehyde (DOPEGAL, MAO product of norepinephrine) (Grünblatt & Riederer, 2014). A constant exposure to both, biogenic and xenogenic aldehydes contributes to the total aldehydic load in the neurons which, combined with mitochondrial dysfunction can lead to the neurological diseases previously mentioned. In this context, aldehyde dehydrogenase 2 (ALDH2), one of the most efficient human cell´s enzymes in metabolizing biogenic aldehydes, plays a crucial role in maintaining a proper metabolism by detoxifying cells from these aldehydic substrates (Chen et al., 2014). However, reactive aldehydes accumulation may inhibit ALDH2 and trigger mitochondrial dysfunction leading to a higher aldehyde-induced damage in several brain areas (Goldstein et al., 2013).

1.1 Search Strategy and Selection Criteria

Authors searched for peer-reviewed articles in PubMed database, Google scholar search platform, and Elsevier DataSearch. We considered articles including the most recent and remarkable studies in the field. The search terms were: "aldehyde dehydrogenase 2", "mitochondrial dysfunctions", "oxidative stress", "neurodegenerative diseases", "Parkinson´s disease", "Alzheimer´s disease", "genetics", "proteins", "cellular lines", "animal models". Additional articles were identified by searching the reference lists of identified reviews that provided insightful or comprehensive overviews on relevant aspects of the importance of detoxification in neurodegenerative diseases.

1. Aldehyde dehydrogenase 2 in health and disease

Aldehyde dehydrogenase (ALDH) superfamily is constituted by 9 families with 19 isozymes known for playing a crucial role in several biological processes through development and senescence as well as detoxification pathways in the organism. They

are expressed in several subcellular compartments including the mitochondria, endoplasmic reticulum (ER), nucleus and cytosol in different tissues, such as gastric mucosa, heart, lungs, liver, retina, and brain (Alnouti et al., 2008). Among their functions, they catalyze $NAD(P)^+$-dependent and irreversible oxidation of biogenic and exogenous aldehydes, to their corresponding carboxylic acids, some of them essential products for numerous cellular processes (Vasiliou et al., 2004). Additionally, ALDHs exert non-enzymatic functions, acting as binding proteins for various compounds as hormones and cholesterol. Furthermore, they may have important antioxidant roles in NAD(P)H production, UV light absorption and the scavenging of hydroxyl radicals (Marchitti et al., 2008).

Both, ALDH1A1 and ALDH2 are involved in ethanol-derived acetaldehyde (ACD) oxidation to acetic acid, sharing a 68% amino acid similarity despite cytosolic ALDH1A1 having less affinity for ACD (Km 50-180 μM) than mitochondrial ALDH2 (Km < 1 μM) (Marchitti et al., 2008). In particular, ALDH2 is highly expressed in several tissues including heart, liver and brain (Alnouti et al, 2008). In addition to the dehydrogenase function, ALDH2 also exhibits esterase and relevant nitrate reductase activity for nitrate bioactivation, including nitroglycerin formation (Marchitti et al., 2008; Vasiliou et al., 2013). The ALDH2 substitution of Glu487 for Lys487, (ALDH2*2) is the most common and best studied single point mutation in humans that encodes an inactive mitochondrial isozyme and it is carried by nearly 50% of Asiatic population (Zhang et al., 2015). This mutation results in a deficient NAD(P) binding site with affected kinetic properties of the enzyme (Koppaka et al., 2012; Larson et al., 2007).

Moreover, ALDH1A1 and ALDH2 are also involved in the metabolism of catecholamines, such as dopamine (DA), norepinephrine (NE) and epinephrine (EPI), due to their expression in relevant brain regions. (Grünblatt & Riederer, 2014). Importantly, the cytosolic enzyme ALDH1A1 is strongly expressed in DA neurons of the ventral tegmental area (VTA) and substantia nigra (SN) playing a role in the maintenance of dopaminergic system integrity (Anderson et al., 2011). It has been thus pointed-out that ALDH1A1 and ALDH2 may metabolize DA-derived aldehydes in a complementary fashion, although other isoenzymes participation cannot be ruled-out (Marchitti et al, 2007).

Thus, in brain DA is oxidized to 3,4-dihydroxyphenylacetaldehyde (DOPAL) in close apposition to the outer membrane of the mitochondria due to the MAO localization in this organelle (Doorn et al., 2014). DOPAL is mainly degraded by ALDH to 3, 4-dihydroxyphenylacetic acid (DOPAC) and finally converted by the enzyme catechol O-methyltransferase (COMT) to homovanillic acid (HVA), the final product of DA metabolism (see Marchitti et al., 2007 for an extensive review of DA metabolites). In contrast, NE and EPI are first converted into DOPEGAL whose metabolism occurs primarily by a reductive pathway that involves aldehyde reductases enzymes (AR). It is known that both, DOPAL and DOPEGAL are highly reactive and toxic bioproducts capable to pass through the cell membrane and condense with numerous molecules inducing damage into the brain integrity and disrupting homeostasis, affecting thereby

neurotransmission-related events. It has been shown that DOPAL induces cell death *in vitro* (Burke et al., 2004) and *in vivo* (Burke et al., 2003), produces aggregation and adduct formation of alpha-synuclein (Burke et al., 2008; Follmer et al, 2015), disrupts neurotrophic cell signaling (Kang et al., 2017) and promotes ROS formation and enhanced cross-linking of protein, probably as a result of its oxidation to a semiquinone radical and to an *ortho*-quinone (Anderson et al., 2011). Moreover, DOPAL disrupts the mitochondrial functionality by inducing the permeability transition (PT) of isolated mitochondria from neuronally differentiated PC12 cells, a cytotoxic effect that was prevented by PT inhibitors (Kristal et al., 2001).

Some authors have ascribed a preponderant role to ALDH2 in DOPAL-detoxification pathways in the dopaminergic circuit (Doorn et al., 2014; Florang et al., 2007). The ROS and toxic aldehydes generated by DA metabolism lead to increased levels of cellular oxidative stress, lysosomal as well as mitochondrial damage, NAD + depletion and DNA-directed alterations all of which are the main cause of neuronal injury and dysfunction which in turn induce apoptosis in the affected neurons (Burbulla et al., 2017; Adams et al., 2001).

In this regard, it is known that oxidative stress triggers lipid peroxidation increasing 4-HNE levels with resulting mitochondrial dysfunction due to a decrease in the membrane potential of this organelle. Importantly, 4-HNE, a derivative aldehyde generated by the reaction of superoxide with unsaturated fatty acid is oxidized with high efficacy by ALDH2 (Breitzig et al., 2016).

In this framework, mutations and polymorphisms of ALDH2 which lead to an impaired enzymatic function are the basis of several pathological conditions due to the accumulation of cytotoxic aldehydes, including 4-HNE, a toxic bioproduct associated to aging and neurodegenerative diseases (Chen et al., 2015; Wey et al., 2012). These pathologies are characterized by impairments of cell metabolism and regulatory processes including mitochondrial dysfunction, vesicular transport alterations, lipid peroxidation, protein cross-linking and oxidative stress. All these events may be the consequences of an excessive aldehyde accumulation as is proposed by the ***catecholaldehyde hypothesis of neurodegeneration*** (Panneton et al., 2010; Goldstein et al., 2013.; Casida et al., 2014). In the context of this hypothesis, the role of the enzyme ALDH2 in the most prevalent neurodegenerative disorders in humans, i.e. Alzheimer´s and Parkinson´s disease will be discussed in the following sections.

2. Alzheimer's Disease

In 1906 Dr. Alois Alzheimer described the spectrum of a "presenile dementia" and observed two major pathological processes i.e. amyloid beta (Aβ) and Tau protein deposition that still remain as the main explanation of the pathogenesis of Alzheimer´s Disease (AD) (Sery et al., 2013). Nowadays, AD is the most common neurodegenerative disease worldwide, where aging constituted the major risk factor. It is characterized by synapse loss (predominantly within the neocortex area) and by the presence of certain

distinctive lesions as a consequence of protein misfolding throughout the brain (Chang et al., 2014).

As many neurological diseases, AD is linked to oxidative stress, which is considered the most common effector of the cascade of the degenerative events (Benedetti et al., 2014). Oxidative stress can be evidenced in the blood, cerebrospinal fluid (CSF), and brain of neurologic patients with probable AD diagnosis (Chang et al., 2014). The appearance of early oxidative stress markers in these patients and in animal models of AD before either cognitive dysfunction or Aβ plaques and intracellular neurofibrillary tangles become apparent, suggests that oxidative damage may be a primary event in AD pathogenesis (D´Souza et al., 2015). In this context, ROS play a key role in lipid peroxidation, resulting in the formation of many aldehydic products, like 4-HNE which is considered one of the fundamental signaling molecules in the pathogenesis of AD (Benedetti et al., 2014; Bradley et al., 2010; Butterfield et al., 2011). Like other aldehydes, 4-HNE detoxification depends on ALDH2 activity provided that its inhibition increases the vulnerability to 4-HNE induced damage (Bradley et al., 2010). A more profound knowledge of these mechanisms will provide new insights regarding therapeutic approaches that may prevent or reverse AD progression.

High ALDH2 protein levels are found in the central nervous system and peripheral tissues. Its activity is more intensively studied in reference to the mechanisms involved in ALDH2 alterations in AD brains (Michel et al., 2010). As we previously described, ALDH2 is a known target for oxidation under conditions of oxidative stress (Ohsawa et al., 2003). Several studies reported its association as a neuroprotective enzyme against oxidative stress and neurodegeneration and its deficiency as a risk factor for elevated oxidative stress and subsequent AD development (Singh et al., 2010; Ohta et al., 2004). *Poon et al.* described molecular events associated with the aging olfactory system and its correlation with AD. They report a comparative proteomic analysis of age-related differences in expressed proteins of the olfactory epithelium (OE) and olfactory bulb (OB) of old (80-week old) and young (6-week old) mice. In these studies, they found that ALDH2 protein levels were down-regulated in the OE of old mice compared to young mice, which may result in an increased susceptibility to oxidative stress in the old mice's OE (Poon et al., 2005). Previous reports found increased ALDH2 levels in the cerebral cortex of AD patients, where the immunoreactivity was prominent in senile plaques in the temporal cortex (Picklo et al., 2001). *Michel et al.* found an increase of ALDH2 activity in the putamen of these patients, but no differences were detected in the frontal cortex (Michel et al., 2010).

3.1 Molecular Alterations

Genetic aberrations account for only a small proportion of AD cases (<5%) and only a few of them are related to mitochondrial dysfunction and a correlation of oxidative stress to aldehyde detoxification. Several reports of genetic modifications, such as genome-wide association studies (GWAS) and single genetic association studies, have reported gene variation on ALDH2 in East Asian patients (Hao et al., 2011). In this respect, *Ma et al.* (2016) investigated the association between ADH1B rs1229984 and ALDH2 rs671

polymorphisms and the development of Alzheimer's disease in a Chinese population. Regarding ALDH2 rs671, the AA genotype was correlated with an increased risk of Alzheimer's disease as compared to the GG genotype and associated with Alzheimer's in both dominant and recessive models. In addition, the Glu504Lys single nucleotide polymorphism (SNP) of the ALDH2 gene, which affects ALDH2 enzymatic activity leading to accumulation of toxic aldehydes such as ACD, is a potential candidate genetic risk factor for a variety of chronic diseases such as cardiovascular disease, cancer, and late-onset Alzheimer's disease (Zhao & Wang., 2015; Li et al., 2009), interacting synergistically with the presence of the apolipoprotein E allele 4 (APOE ε4) (Kamino et al., 2000; Ohsawa et al., 2003; Ohta et al., 2004; Kim et al., 2004; Wang et al., 2008).

On the other hand, the association between the mutant allele of mitochondrial aldehyde dehydrogenase (ALDH2*2) and Alzheimer's disease (AD) has been controversial during the last decades. Meta-analysis studies and the database www.alzgene.org showed that the ALDH2 genotype was not found to be associated with increased AD risk. Among these studies, *Shin et al*. investigated the longitudinal association between ALDH2*2 and AD incidence, reporting no significant associations among the ALDH2*2 and any cognitive outcomes (incidence of dementia or cognitive decline) (Shin et al., 2005). Similarly, in a Mongolian population, the ALDH2 gene may not represent a risk factor in the development of AD provided that its correlation with APOE ε4 displays no disparity (Zhou et al., 2010). Furthermore, a case-control study of the Japanese population associated or not with high alcohol consumption was not able to find any significant association of ALDH2 polymorphisms and dopamine β hydroxylase genes with AD risk (Komatsu et al., 2014).

3.2 In vitro and In vivo models

Cellular models are an appropriate approach to reproduce and understand the functional effects of specific genetic polymorphisms. For example, *Ohsawa et al.* demonstrated that the presence of the ALDH2*2 gene in PC12 cells resulted in the suppression of mitochondrial but not cytosolic ALDH activity in these cells, which were highly vulnerable to exogenous 4-HNE (Ohsawa et al., 2003). Furthermore, the treatment of human endothelial cells with amyloid β peptides induced loss of mitochondrial membrane potential, increased cytochrome c release and ROS accumulation, events that were associated with 4-HNE accumulation and a 40% decrease in ALDH2 activity. A selective ALDH1A1 and ALDH2 activator, Alda-1 (Kotraiah et al., 2013) abolished this 4-HNE accumulation and may have reduced endothelial injuries, preserving the angiogenic potential of the endothelium, mainly in the amyloid angiopathy (Solito et al., 2013). Furthermore, in primary rat hippocampal neurons, the increased expression of ALDH2 protected the neurons against 4-HNE-induced neurite damage and resultant oxidative stress (Bai & Mei., 2011).

On the other hand, the study of late-onset/age-related AD etiology has been hampered by a paucity of animal models. *D´Souza et al.*, hypothesized that in mice lacking ALDH2 4-HNE accumulates and causes the appearance of AD-like pathological changes including increases of amyloid-beta, p-tau, activated caspases and the decrease of synaptic proteins

in hippocampal slices and brain atrophy leading to cognitive dysfunction in behavioral tests, pathological manifestations that are rarely observed in current AD animal models (D´Souza et al., 2015). Nevertheless, Ohta and Ohsawa found similar results in mice of 18-months-old knock-out for ALDH2 (Ohta and Ohsawa., 2006) while the correlation between cognitive impairment and degeneration was accelerated by APOE knock-out two years later (Ohsawa et al., 2008).

These lines of evidence were taken into consideration to create a double-transgenic AD mouse model to explore the pathological and behavioral effects of oxidative stress (Kanamaru et al., 2015). In this opportunity, mice who express a mutant form of the human amyloid precursor protein (APP) were crossed with DAL mice expressing a dominant-negative mutant of mitochondrial ALDH2. They observed that the life-span of APP/DAL mice was significantly shorter than their control APP or DAL counterparts while this double-transgenic mouse also showed accelerated amyloid deposition, tau phosphorylation and gliosis (Kanamaru et al., 2015).

3. Parkinson´s Disease

Two hundred years have passed since James Parkinson published *An Essay on the Shaking Palsy* where he first described the neurological disorder that today bears his name (Przedborski., 2017). Parkinson´s disease (PD) has become the second most common neurodegenerative disorder after AD and its etiology remains unclear. It is characterized by the progressive loss of dopaminergic neurons in the *susbtantia nigra pars compacta* (SNpc) projecting to the putamen and caudate nucleus of the brain (Schapira et al., 2017). This dopaminergic deficiency within the basal ganglia leads to parkinsonian cardinal motor symptoms including rigidity, bradykinesia and tremor. However, PD is also associated with numerous non-motor symptoms (cognitive dysfunction, neuropsychological symptoms, sleeping disorders, etc.) with some preceding the motor dysfunction for more than a decade (Kalia et al., 2015).

It is now known that PD involves multiple neuroanatomical structures with an etiology resulting from the interplay between genetics and environment, with more prevalent environmental origins. Treatments to relieve the symptoms aim to increase DA concentrations or to stimulate DA receptors. Among the multiple hypotheses for PD´s etiology, oxidative stress and aldehyde-related toxicity are major components in the pathophysiology of this disorder (Michel et al., 2014; Grünblatt & Riederer, 2014). The increased ROS production and resultant oxidative stress could lead to cell death and degeneration. These molecules stimulate the production of aldehydes which may be toxic if ALDH activity is reduced, particularly ALDH1A1 and ALDH2, as we mentioned, are crucial in the deposition of neurotoxic metabolites, such as DOPAL and DOPEGAL. Concerning this aspect, when injected into ventrotegmental area (Burke et al., 2003) or into the substantia nigra (SN) (Panneton et al., 2010) DOPAL was neurotoxic to the DA neurons supporting the role of this catecholamine-derived aldehyde in PD etiology.

Furthermore, 4-HNE and malondialdehyde (MDA), have been found to be significantly increased in post-mortem SN of PD patients. Interestingly, although 4-HNE is a substrate of ALDH2, the enzyme can also be inactivated by 4-HNE by covalently adducting to the

Cys in the catalytic site of the enzyme, which in turn increases DOPAL levels, thereby interlinking the oxidative stress and the catechol aldehyde hypothesis (see Chen et al., 2014 and Florang et al., 2007).

Thus, the studies of genetic modifications in cellular and animal models are crucial to understanding the specific pathogenesis of PD and therefore important to identify potential targets and or therapeutic-related approaches intended to relive the severe symptoms that affect the life quality of these patients.

4.1 Molecular Alterations

Large genome-wide association studies (GWAS) have identified more than two dozen common genetic variants for PD, each with a relatively small effect size; in combination with rare Mendelian genes, genetics account for at most 10–20 % of PD (Ritz et al., 2016). Although there is no ALDH2 gene variation in the different databases determined as a risk factor for PD development, it was reported that an Asian specific single nucleotide polymorphism, rs671, causes reduced enzymatic activity. Thus, PD patients with reduced ALDH2 activity owing to this polymorphism are at risk for neuropsychological impairments (Yu et al., 2016). In addition, other ALDH2 polymorphisms (haplotype of rs737280, rs968529, rs16941667, rs16941669, rs9971942) have been reported and associated with the exacerbation of PD risk (Fitzmaurice et al., 2014). In a Chinese cohort, ALDH2 tag-single nucleotide polymorphisms, including rs4767944, rs441, and rs671, were extracted and analyzed, with the results suggesting an association between PD susceptibility and ALDH2 polymorphisms (Zhang et al., 2015). Nevertheless, in an analysis of genotype distributions in an Iranian PD patient population, no significant relationships were observed between rs4767944 polymorphism of the ALDH2 and PD (Madadi et al., 2016). *Zhao et al.* studied the role of ADH2 Arg47His and ALDH2 Glu487Lys genetic polymorphisms in PD development in a Chinese population. The ALDH2 Glu487Lys polymorphism in the dominant, co-dominant or recessive models were found to be significantly associated with the elevated risk of PD (Zhao et al., 2015). Moreover, a differential expression in ALDH2 activity according to the brain regions analyzed was reported with an increased activity of this enzyme in the putamen of PD patients while no significant differences in the frontal cortex area were informed (Michel et al., 2014).

4.2 In vitro and In vivo models

PD is believed to be caused by genetic factors, environmental exposures and their interactions (Zhang et al., 2015; Fitzmaurice et al., 2014). *Wey et al.* hypothesized a decreased function of ALDH2 consequential to exposure to environmental toxins and its correlation with this neuropathology. To prove their hypothesis, they generated mice null for ALDH1A1 and ALDH2 and observed significant increases in biogenic aldehydes reported to be neurotoxic, including 4-HNE and DOPAL. Consequently, this knock-out animal model could be useful to understand impaired detoxification of biogenic aldehydes and its importance in the pathophysiology of PD (Wey et al., 2012). Moreover, the activation of ALDH2 could be a neurotherapeutic approach for PD, since it plays a

crucial role in maintaining mitochondrial normal function to protect against neurotoxicity. Additionally, in some parkinsonism´s animal models, the intraperitoneal administration of Alda-1, a potent activator of ALDH2 reduced significantly cell death in dopaminergic neurons, induces a decrease in ROS accumulation, a reversal of mitochondrial membrane potential depolarization, and an inhibition of the activation of proteins related to the mitochondrial apoptotic pathway (Chiu et al., 2015). Alternatively, trapping agents such as hydralazine may prevent adduct formation (Burcham & Pike., 2006) or prevent cognitive damage by the administration of deuterium-reinforced polyunsaturated fatty acids that would mitigate lipid peroxidation-induced oxidative damage (Elharram et al., 2017).

4. Conclusion

Evidence presented in this review provides new insights regarding the importance of ALDH2 and its relationship with the two most common neurodegenerative diseases. In the last decades and with the development of state-of-the-art technologies, novel neurochemical circuits have been described, a fact that contributed to clarifying the knowledge of the cellular and molecular mechanisms involved in neuropathology and neurodegeneration (Figure 1). Compelling reports have attributed to brain-generated 4-HNE a key role in chronic neurodegenerative insults. Moreover, the main mitochondrial enzyme in charge of its detoxification, ALDH2 needs to be further studied taking as well into consideration the numerous polymorphisms present worldwide, particularly in the Asiatic population. Thus, to sum up, ALDH2 could be a potential target in new therapeutic approaches for PD and AD provided its crucial role in mitochondrial normal function maintenance that is required to protect against aldehyde-induced neurotoxicity.

Declaration of Interest

The authors report no conflicts of interest on any front.

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Figure Legend

Figure 1. Role of ALDH2 in the cellular events that determine the health vs disease status of the neuronal environment.
Boldness and size typography denotes putative differences in expression and in/or functionality of the enzyme.